UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,615	12/04/2003	Vivek M. Rangnekar	028750-225	5759

21839 7590 01/11/2007
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/726,615	RANGNEKAR, VIVEK M.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 7-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1, 2, 6 and 24) in the reply filed on 11/3/06 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-VIII are closely related and a search of any claims should by necessity require a proper search of the others.

This is not found persuasive because as the MPEP teaches "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That prima facie showing may be rebutted by appropriate showings or evidence by the applicant" (see MPEP 803). In the instant case, the inventions have been shown to be classified differently and the different groups shown to comprise divergent subject matter for which a search for art pertaining to each group is not coextensive. For example, a search for the Par4 polypeptides requires a search that is distinct from that of an antibody against Par4 and a search for Par4 protein would not overlap a search for antibodies binding Par4. Antibodies binding Par4 may be known even if the polypeptide were not. For each of the distinct groups a search burden has been similarly determined to exist as set forth in the restriction requirement mailed 10/6/06. Because the inventions are separately classified have a separate status in the art as demonstrated by the different fields of search required to search each of them, a serious burden exists in examining all of the claims. The requirement is still deemed proper and is therefore made FINAL.

Claims 3-5 and 7-23 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/3/06.

Claim Objections

Claims 6 and 24 objected to because of the following informalities: they are drawn to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over Par-4 proteins that exist naturally because the claims do not particularly point out any non-naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor , e.g. by insertion of "Isolated" or "Purified"

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2, 6 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of "resistant to Par-4" are unclear. While applicants recite that the tumors are resistant to Par-4, it is not clear how a tumor can be resistant to Par-4, which is a protein. As applicants have not indicated what about Par-4 the cells are resistant to, the metes and bounds of the tumors cannot be established.

Claim 2 is vague and indefinite in that the metes and bounds of "1-204, 137-221, 137-213, 137-198 and 137-195" are unclear. First, it is unclear of recitation of "1-204, 137-221, 137-213, 137-198 and 137-195" is intended to indicate specific reference amino acids. If applicants' recitation of mutant Par-4 proteins is in reference to amino acid positions and, therefore, a reference sequence is required to practice the claimed invention. However, there is no reference sequence provided in the specification or the claims to know the actual amino acids encompassed by recitation of "1-204, 137-221, 137-213, 137-198 and 137-195".

Claim 6 is vague and indefinite in that the metes and bounds of "encoded by a nucleic acid contained in one or more sequences of clam 3" are unclear. It is not clear if the isolated polypeptide of claim 6 must comprise at least one dinucleotides that is in common with one or more of the sequence i.e. a consensus sequence or if the polypeptide is the product of chimeric sequences each obtained separately from one or more sequences of claim 3.

Claim 24 recites the limitation "the amino acid sequence of claim 3" in claim 24. There is insufficient antecedent basis for this limitation in the claim. Claim 3 is drawn to a nucleotide sequence and hence does not recite an amino acid sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The claims are drawn to a modified Par-4 comprising at least one substitution wherein the modified Par-4 is effective in reducing the size of tumors resistant to Par-4. As well the modified Par-4 "comprises" a mutant of Par-4 that is selected from 1-204,

137-221, 137-213, 137-198 and 137-195. Finally the claims are drawn to an isolated peptide comprising at least 5 amino acids comprising *a* sequence encoded by the polynucleotides encoding 1-204, 137-221, 137-213, 137-198 and 137-195. The invention utilizes disciplines of molecular biology and protein chemistry.

2) **Scope of the invention**. Structurally, the nomenclature 1-204, 137-221, 137-213, 137-198 and 137-195 translates into peptides that have been deleted of all but a core region applicants have identified as a death domain. Actual substitution of any amino acids within Par-4 are not so described in the specification. The specification teaches, apoptosis -resistant androgen dependent prostate cancer cells LNCaP, LAPC4 and MDA 2b, mouse immortalized fibroblast NIH 3T3 cells, and primary prostate epithelial cells PrE or primary prostate stromal cells PrS".

3) **Number of working examples and guidance**. The specification teaches identification of a unique core domain that is 59 amino acids and localized to between position 137 and 195 of "the wild-type Par-4" protein. This region contains a nuclear localization sequence, which is sufficient and necessary to induce apoptosis in Par-4 resistant cancer cells as well as Gas pro death pathway activation. Par-4 mutants deleted of the nuclear localization signal at 147-153 did not enter the nucleus and did not lead to apoptosis of PC3 cells. And Par-4 mutants 1-204, 137-221, 137-213, 137-198 and 137-195 lead to apoptosis in transient transfections in several cancer cells but not the corresponding normal cells. A panel of androgen dependent or independent prostate cancer cells, immortalized cells and primary cells were tested. Apoptosis was induced in androgen dependent and independent cells but not the normal or immortalized cells (see Table 1 and 2). As well applicants disclose that fragments 5 amino acids or greater can be used to assemble a functional full polypeptide (see e.g. bridging ¶page 26-27).

4) **State of Art**. A review of the art demonstrates that the ability to *de novo* protein model is not routine but requires vast computation skills (see Protein structure prediction, page 2, first paragraph). This article also teaches that prediction methods that rely on comparative protein modeling allow similar domains or structures to allow identification of three-dimensional models (see Protein structure prediction, page 2, first paragraph). However, as demonstrated by Smith et al, even a single mutation can greatly effect even simple structural formations of the resultant protein. This is explained in the review titled Tertiary structure that teaches mutations in genes encoding proteins can result in degradation or lack of transport or aggregation into insoluble deposits of the resulting protein (begin page 1, last paragraph). A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness (see Tertiary structure, Protein structure prediction and Smith et al). Therefore, the ability to predict *a priori* which sequences that are identified following hybridization will meet a particular goal must be considered to be poorly developed.

5) **Unpredictability of the art**. The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I.

duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the broad nature of the claims as broadly drawn to any Par-4 containing peptide listed below.

1) Applicants reference a broad and diverse genus of proteins known as Par-4 whose modification may or may not result in effectiveness is reducing the size of tumors resistant to Par-4. Furthermore, the substitutions are said to be in the amino acid sequence of a precursor Par-4 sequence, which exacerbates the ability to identify the sequence intended as Par-4. By referencing "a precursor Par-4", the reference sequence becomes even more confusing. The art teaches a variety of diverse proteins known as Par-4 proteins ranging from AAD45355 from *C. elegans* that is a 617 amino acids putative serine-threonine kinase to multiple human proteins. Three proteins from *Homo sapiens* identified as Par-4 include BAC99030 (121 amino acid) prostate apoptosis response protein, NP_002574 (340 amino acids) and Q62627 (332 amino acid) the later two proteins listed as PRKC apoptosis proteins. Fewer sequences known as "precursor Par-4' are identified. Given the recitation in claim 2 to specific deletion mutants, 1-204, 137-221, 137-213, 137-198 and 137-195, without providing a reference sequence engenders a level of difficulty in identifying the proper "core" that is meant to be contained within 1-204, 137-221, 137-213, 137-198 and 137-195. These positions become artificial landmarks without an indication as to what sequences can or are contained within them. In light of the art at the time of filing, the instant invention would require undue experimentation to identify modified Par-4 proteins as broadly recited.

2) Applicants refer broadly to a Par-4 that is modified. In base claim 1, the modified Par-4 appears to be drawn to a protein comprising a substitution in its amino acid sequence as compared to precursor Par-4 sequence such that modified Par-4 is effective in reducing the size of tumors resistant to Par-4. Thus the claims recite broadly that the modified Par-4 comprises any substitution of any amino acid residue in any precursor Par-4 sequence. By recitation of at least one substitution a broad and diverse genus of peptides with substitutions of as little as one amino acids to substitution of multiple amino acids within the protein are encompassed. However, the efficacy of the peptide is based upon its pro-apoptotic activity in cancer cells, which is described as the result of deletion of sequences outside of the critical "death domain". Applicants do not teach any substitutions in Par-4 nor do applicants provide structural requirements other then the core domain such that a person of skill in the art would know what amino acids can be substituted in any Par-4 protein. Hence, it would require undue experimentation to determine those amino acids in the precursor protein of any Par-4 protein that can be substituted in order to lead to reduction of tumor size of Par-4 resistant tumors given the lack of guidance in the specification.

3) Finally, in claim 6, applicants claim a genus of peptides that are said to he at least five amino acids long and comprises a sequence encode by any of the 1-204, 137-221, 137-213, 137-198 and 137-195 mutant polynucleotide sequences. Thus a genus of peptides are recited that are only limited by comprising at least 5 amino acids in which a sequence is encode by a nucleic acid contained in a Par-4 mutant sequence. The specification discloses that such a polypeptide can be used in combination with other peptides to form a fully functional Par-4 peptide. As so

disclosed, only fragments completely homologous to Par-4 are consistent with the claimed invention have an enabled use.

6) **Summary**. Given the broad nature of the recited modified Par-4 proteins and the unknown nature of the amino acid sequence and the unknown numbers of substitutions, the invention has a high level of unpredictability. The specification does not disclose the reference sequence. As well, while the claims recite a Par-4 comprising substitutions of amino acids residues, the specification does not disclose any modifications of Par-4 that are the result of substitution. Rather, the specification discloses a Par-4 peptide that has been modified to induce apoptosis in tumors resistant to Par-4 are the result of deletion of amino acids surrounding a core sequence of "137-195" which particularly must embrace deletions of the C-terminus leucine-fingers. Hence, the specification does not disclose any substitutions that result in peptides effective against Par-4 resistant tumors. Rather, the specification only discloses that deletion of the C-terminus leucine-fingers have an enabled use in inducing apoptosis in Par-4 resistant tumors. Exacerbating the unpredictability of identifying substitutions is the lack of disclosure of the reference sequence for mutants 1-204, 137-221, 137-213, 137-198 and 137-195. As the claims do not identify the source of the Par-4 peptide, it is not clear to what sequences 1-204, 137-221, 137-213, 137-198 and 137-195 correspond. While the specification teaches that the particular Par-4 peptide of the instant invention has 332 amino acids and the modified peptide must comprise 1-204, 137-221, 137-213, 137-198 and 137-195, it is highly unpredictable that the sequences corresponding to 1-204, 137-221, 137-213, 137-198 and 137-195 can be identified for any Par-4 peptide given the wide and variable sequences known as Par-4. Even if the sequence could be said to be limited to Q62627, which is 332 amino acids, and this sequence comprises

the "death domain" within amino acids 1-204, 137-221, 137-213, 137-198 and 137-195, the claims are drawn to a modified Par-4 in which at least one amino acid is substituted. Modification of even as little as one amino acid has the potential to effect the function of the protein as taught by Tertiary structure, Protein structure prediction and Smith et al especially as the specification does not teach the structural properties of Par-4 amino acids that can be substituted. In view of predictability of the art to which the invention pertains and the lack of guidance and the inability to predict sequences required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Guo et al (Nature Medicine, 1998, pages 957-962; see entire document).

Guo et al teach Par-4 protein that comprises substitutions in amino acid sequences as compared to full length Par-4 in that sequences comprising for example termination signals are replaced with leucine zipper sequences (Par-4-Leu-Zip) or substitution of the C-terminal region for termination sequences (Par-4-Δleu-Zip), see figure 3. This modified Par-4 peptide exhibits effectiveness in inducing apoptosis of cells previously non-apoptotic in the presence of Par-4 absent inducer as evidenced in figure 3 as recited in claim 1. These peptides comprise at least five amino acids with several sequences encoded by the nucleic acid of 1-204 mutants as recited in claim 6. While claim 24 recites that the pharmaceutical composition comprises a Par-4 mutant protein sequence of claim 3, claim 3 is drawn to nucleic acid. Thus claim 24 is interpreted to intend that the nucleic acid sequences of claim 3 encode the Par-4 mutants included in the pharmaceutical composition. Based upon this interpretation and given the broadest possible interpretation of a carrier, the teachings of Guo et al teach that the Par-4 mutants were delivered with Lipofectamine (see e.g. page 959, col 2, ¶ 1) can be said to read on a composition of Par-4 in acceptable diluent and carrier as recited in claim 24.

Claim 6 is rejected under 35 U.S.C. 102(e) as being anticipated by Darrow et al (US 2006/0141451; see entire document).

Darrow et al teach a chimeric peptide, which comprises substitution of one Par-4 sequence for another with the goal of combined functions of the combined domains

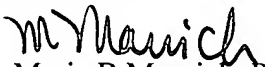
Darrow et al teach peptides with at least 5 amino acids in which the peptide comprises at least one sequence that is also found in the mutant Par-4 sequences recited as 1-204, 137-221, 137-213, 137-198 and 137-195 given that as shown in figure 2 and embraced n the specification at for example ¶ 0009 which discloses a fragment of at least 15 amino acids corresponding to amino acids 219 to 243 of SEQ ID NO:3 (Par-4), the sequences comprise Par-4 sequences as recited in claim 6.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Maria B Marvich, PhD
Examiner
Art Unit 1633